Request for permission for oral testimony at Idaho Medicaid's P&T Committee meeting on 05-11-2012

Submission # 3

As of April 26, 2012, this request has been:

- o Approved
- X Denied

Request for permission for oral testimony at Idaho Medicaid's P&T Committee meeting on 05-11-2012

Submission # 3

As of April 23, 2012, this request has not been reviewed yet.

Gennrich, Jane - Medicaid

From: Eide, Tamara J. - Medicaid
Sent: Monday, April 16, 2012 9:05 AM
To: Gennrich, Jane - Medicaid
Subject: FW: Updated Information
Attachments: AVONEX Idaho Medicaid Update.pdf; Matson_ Dose Titration_CMRO_2011.pdf; Phillips Autoinjector Paper.pdf; Avonex Prescribing Information_ 022712_FINAL.pdf

Tami Eide, Pharm.D., BCPS
Medicaid Pharmacy Program Supervisor/Manager
Idaho Department of Health and Welfare
eidet@dhw.idaho.gov
3232 Elder St.
Boise, ID 83705
208-364-1829
800-327-5541 fax

From: Sharon Cahoon-Metzger [mailto:Sharon.Cahoon-Metzger@biogenidec.com]
Sent: Friday, April 13, 2012 10:16 PM
To: Eide, Tamara J. - Medicaid
Subject: Updated Information

Hello Tami,

In preparation for the upcoming Idaho State Medicaid P&T review of the Multiple Sclerosis class on May 11, 2012, please find attached the following information:

1. One-page summary of Avonex clinical information and label changes (effective February 2012)
2. Publication of the clinical trial on Avonex titration (Matson MA, Zimerman TR, Tuccillo D., et.al. *CMRO*. 2011:12:2271-2278)
3. Publication of the clinical trial on Avonex autoinjector pen (Phillips JT, Fox E, Grainger W., et.al. *BMC Neurology*. 2011:11:126)
4. New Avonex PI (February 2012)

I have followed the prescribed guidelines for submitted materials and hope that you find this submission acceptable.

There was an update to the Tysabri label in January 2012 as well, but it is my understanding that Tysabri is not being covered on May 11. If this is not the case—i.e. Tysabri will be covered—please advise asap and I can provide that updated information as well.

Please do let me know if there is anything additional I can provide. I hope to share this information with the committee in Boise on May 11.

Kind regards,

Sharon

Sharon M Cahoon-Metzger, PhD
Medical and Outcomes Science Liaison

Biogen Idec Medical Affairs
Office: 801-553-9906
Cell: 916-217-0142

AVONEX®(interferon beta-1a)

Updates to clinical information for MS Class Review

AVONEX is an FDA approved therapy indicated to treat relapsing forms of Multiple Sclerosis (MS). AVONEX is a 166 amino acid glycoprotein produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence is identical to that of natural human interferon beta.

AVONEX is FDA-approved for relapsing forms of Multiple Sclerosis to:
Slow the accumulation of physical disability

- 37% reduction in disability progression sustained over 6 months

Decrease the frequency of clinical relapses

- 32% reduction in annualized relapse rate for those patients completing 2 years of therapy

Use in patients who have experienced a first clinical episode

- 44% reduction in development of Clinically Definitive MS (CDMS) vs placebo at 3 years (unadjusted), p=0.002 and 51% reduction vs placebo adjusted, p<0.0013

Dosing and Dose Delivery Enhancements (Added to Package Insert February, 2012)

- Flu-Like Symptoms (FLS) are common with interferon-beta product and may present barrier to initiation of therapy or maintaining treatment.
  - Study was conducted to characterize the effects of AVONEX dose titration on FLS with regards to incidence and severity.
  - Results of dose titration split over 4 weeks, (Week 1: ¼ (7.5µg), Week 2: ½ (15µg), Week 3: ¾ (22.5µg) and Weeks 4-8: 30µg full dose) reduced FLS by 76% at 4-6 hrs. post-injection and 37% at 12-15 hrs post-injection versus no titration (30ug given weekly). *Matson page 5 Figure 3*
  - AVOSTARTGRIP™ titration pack is available to be used with AVONEX prefilled syringes.

- AVONEX PEN™ is the first single dose, IM autoinjector with a 5/8" needle, available for long term use in treatment of patients with RRMS.
  - An open-label, 4 week study to evaluate effective use, safety, and patient preference of AVONEX PEN™ was conducted in patients who were stabile on AVONEX prefilled syringes.
  - Overall success rate in utilizing AVONEX PEN was 89%. 88% (7/8) of failures were due to removal of needle cover before extending injector shield. No patient harm or device failures occurred. Safety data collected were comparable to known safety profile of AVONEX prefilled syringe and consistent with post marketing data. *Phillips page 5-6;Table 2*
  - Mean pain score was 1.7 (0 no pain-10 extremely painful) following injection with AVONEX prefilled syringe, and 0.7 by week 3 with AVONEX PEN™. 94% of patients preferred autoinjector over prefilled manual injection. *Phillips page 5*

CMRO

Current Medical Research & Opinion Vol. 27, No. 12, 2011, 1–8

0300-7995
doi:10.1185/03007995.2011.630720

Article FT-0310.R1/630720

Original article
Dose titration of intramuscular interferon beta-1a reduces the severity and incidence of flu-like symptoms during treatment initiation

Mark A. Matson
PRISM Research, Inc., St. Paul, MN, USA

Thomas R. Zimmerman Jr
Dianne Tuccillo
Yongqiang Tang
Aaron Deykin
Biogen Idec Inc., Weston, MA, USA

Address for correspondence:
Aaron Deykin, MD, Biogen Idec Inc., 14 Cambridge Center, Building 6A, Cambridge, MA 02142, USA.
Tel.: +1 617-914-6374;
aaron.deykin@biogenidec.com

Key words:
Flu-like symptoms – Intramuscular interferon beta-1a – Multiple sclerosis – Safety – Titration – Treatment initiation

Accepted: 6 October 2011; published online: 28 October 2011
Citation: Curr Med Res Opin 2011; 27:1–8

Abstract

Background/objective:
Flu-like symptoms (FLS) are common side effects of interferon beta (IFNβ) therapy and can negatively affect the willingness of patients with multiple sclerosis to initiate therapy. Although dose titration is commonly used to reduce the severity and incidence of IFNβ-related FLS during treatment initiation, these benefits have not been confirmed in a well controlled study. The objective of this randomized, dose-blinded, parallel-group study was to assess the effect of dose titration on the severity and incidence of FLS during the initial 8 weeks of once-weekly intramuscular (IM) IFNβ-1a administration.

Methods:
Healthy volunteers were randomized 1:1:1 to one of three IM IFNβ-1a regimens: 3-week titration (weekly quarter-dose increments over 3 weeks to full dose [30 µg]); 6-week titration (biweekly quarter-dose increments over 6 weeks to full dose); or no titration (full dose over 8 weeks). At weekly clinic visits, the severity of each FLS was rated 1 hour pre-injection and 4–6 hours and 12–15 hours post-injection. Study endpoints included post-injection change in FLS severity and post-injection FLS incidence (percentage of subjects with a $\geq$2-point increase in total FLS severity score) at each time point.

Clinical trial registration:
Clinicaltrials.gov identifier: NCT01119677.

Results:
Of 234 subjects enrolled, 194 (83%) completed the study. At 8 weeks, FLS severity was significantly reduced at both post-injection time points with 3-week titration (76% reduction at 4–6 hours, $p<0.001$; 37% reduction at 12–15 hours; $p<0.001$) and 6-week titration (50% reduction at 4–6 hours, $p<0.001$; 32% reduction at 12–15 hours; $p=0.002$) compared with no titration. The incidence of FLS was also significantly reduced at both time points with both titration regimens. Safety profiles for both titration regimens were consistent with the current IM IFNβ-1a label. Study limitations included that there is currently no validated assessment tool for evaluating the severity of FLS, that the study enrolled healthy volunteers, that different proportions of females were randomized to the 3-week-titration group than to the 6-week and no-titration groups, and that evaluation of the potential impact of titration on symptoms occurring substantially later after injection was not part of the study protocol.

Conclusion:
Dose titration during initiation of IM IFNβ-1a reduces FLS severity and incidence in healthy volunteers compared with no titration.

Introduction

Flu-like symptoms (FLS) such as fever, muscle aches, chills, and fatigue are common side effects of interferon beta (IFNβ) treatment and may affect the willingness of patients with multiple sclerosis (MS) to initiate therapy[1,2]. Patients are more likely to experience FLS when initiating IFNβ, and the severity and incidence of FLS tend to decrease over time after continued therapy. The initiation phase of MS treatment is a critical period that can affect patients' views on the long-term acceptability of their therapy, underscoring the need for strategies to reduce treatment-related adverse events such as FLS during IFNβ initiation.

Dose titration, the practice of initiating therapy with a lower starting dose and gradually increasing the dose at defined intervals until the full dose is reached, and pre-treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen are strategies commonly used in clinical practice to minimize FLS during initiation of IFNβ treatment[3,4]. The ultimate goal of these strategies is to improve treatment tolerability and adherence. Several studies have examined the beneficial effects of IFNβ dose titration on FLS and support this clinical practice; however, the generalizability of the results is limited by small sample size ($N < 100$), open-label or retrospective design, and/or lack of a control arm[5–7], suggesting the need for a larger-scale, more robust evaluation of dose titration benefits during the initiation phase of IFNβ treatment.

Once-weekly intramuscular (IM) IFNβ-1a, which has been available since 1996, is indicated for the treatment of patients with relapsing forms of MS to slow the accumulation of physical disability progression and the frequency of clinical exacerbations. Efficacy has also been demonstrated in patients who experience a first clinical episode and have magnetic resonance imaging features consistent with MS[8–10]. Although IM IFNβ-1a is generally well tolerated, FLS have been reported in up to 76% of patients receiving this treatment[8,9,11,12].

In a previous post hoc analysis of an open-label study of 47 MS patients, Brandes and colleagues found that quarter- and half-dose titration of IM IFNβ-1a 30 µg during the initial 6 weeks of therapy reduced the incidence of FLS compared with no titration. To more fully characterize the effects of titration, we conducted a prospectively designed, dose-blinded study to determine whether dose titration reduces the severity or incidence of FLS during treatment initiation of IM IFNβ-1a.

Subjects and methods

Study sample

Healthy male and female IFNβ-naive volunteers aged 18–55 years with no medical condition that could interfere with the interpretation of the results of study assessments, a body mass index (BMI) of 19 to 30 kg/m^2, and a minimum body weight of 50 kg during the screening period (a 4-week period before randomization) were eligible to participate in this study (clinicaltrials.gov identifier: NCT01119677). Female subjects of childbearing potential were required to practice effective contraception during the study and to continue contraception for 30 days after their last dose of study treatment. Subjects were excluded based on a history of flu-like illnesses (e.g., gastroenteritis, upper respiratory infection, or common cold) within 1 month of screening or serious infection (e.g., pneumonia or septicemia) within 3 months of screening. Additional exclusion criteria included a known history or positive test result for hepatitis B, hepatitis C, or HIV; clinically significant abnormality in laboratory or electrocardiogram measures; a history of chronic fatigue syndrome or fibromyalgia, pre-malignant disease, or malignant disease; allergy shot or desensitization therapy within 1 month of day 1 (randomization); or vaccination within 2 weeks of day 1. Women who were pregnant or breastfeeding were also excluded.

This study was conducted at PRISM Research (1000 Westgate Drive, Suite 149, St. Paul, MN, USA) and Dedicated Phase 1 (734 W. Highland Avenue, Phoenix, AZ, USA) in accordance with national and local laws and regulations, the International Conference on Harmonisation guidelines for Good Clinical Practice, as well as the Helsinki Declaration (2008 revision). The study protocol was reviewed and approved by the RCRC Independent Review Board, LLC (2111 West Braker Lane, Suite 400, Austin, TX, USA) and the Liberty Independent Review Board (2024 Larchmont Drive, DeLand, FL, USA). All subjects gave written informed consent before being evaluated for eligibility.

Study design

This randomized, dose-blinded, parallel-group study was conducted at two clinical sites in the United States between 5 May and 25 November 2010. Using a computer-generated list, eligible subjects were randomized 1:1:1 to one of three dose-titration regimens for once-weekly IM IFNβ-1a (Avonex†) (Figure 1). Subjects in the no-titration arm received weekly full-dose (30 µg) IM IFNβ-1a injections from week 1 to week 8. Subjects in the 3-week titration arm were titrated in weekly quarter-dose increments over the initial 3 weeks (7.5 µg [week 1], 15 µg [week 2], 22.5 µg [week 3]), then continued on full dose from weeks 4 to 8. Finally, subjects in the 6-week titration arm were titrated in biweekly quarter-dose increments over the initial 6 weeks (7.5 µg [weeks 1–2], 15 µg [weeks 3–4], 22.5 µg [weeks 5–6]), then continued on full

†Avonex is a registered trade name of Biogen Idec Inc., Weston, MA, USA.

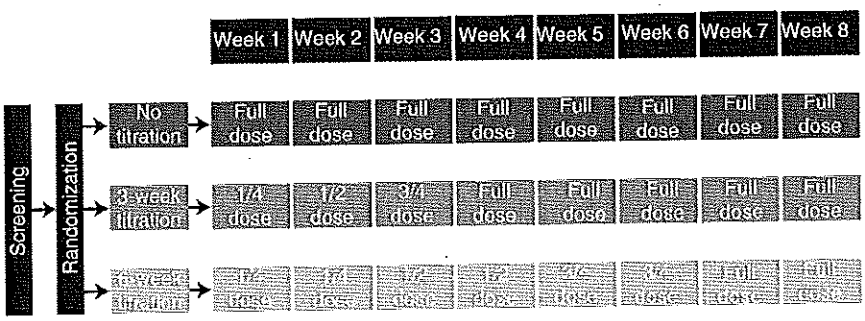

Figure 1. Dosing schedule of 30 μg IM IFNβ-1a.

Table 1. Criteria for assessment of FLS.

Symptom	Score 0	1	2	3
Muscle aches	Absent	Mild: did not interfere with daily activities	Moderate: sufficient to interfere with daily activities	Severe: bed rest required
Chills	Absent	Mild: did not interfere with daily activities	Moderate: sufficient to interfere with daily activities	Severe: bed rest required
Fatigue	Absent	Mild: did not interfere with daily activities	Moderate: sufficient to interfere with daily activities	Severe: bed rest required
Body temperature	<99.1°F <37.3°C	≥99.1°F to <100.1°F ≥37.3°C to <37.8°C	≥100.1°F to <101.1°F ≥37.8°C to <38.4°C	≥101.1°F ≥38.4°C

FLS, flu-like symptoms.

dose during weeks 7 and 8. Each weekly IM IFNβ-1a injection was prepared by the study pharmacist per the unique subject identification number and corresponding titration scheme assignment. Titrated IM IFNβ-1a doses (one-quarter [7.5 μg], one-half [15 μg], and three-quarters [22.5 μg]) were prepared by first emptying pre-filled 30-μg syringes into a mixing vial, then drawing the specified volume (dose) from this solution into a delivery syringe per the assigned titration scheme. For the full 30-μg dose, a pre-filled IM IFNβ-1a syringe was used in accordance with the drug label[13]. Each dose was administered in the clinic by a designated, nonblinded study nurse or health care professional. To maintain dose blinding, subjects and other site study personnel were not allowed to watch the injections. Weekly IM IFNβ-1a injections were administered at approximately the same time of day across all dosing visits, and within ±2 hours of the first injection time on day 1. All subjects were administered prophylactic acetaminophen 650 mg within 1 hour prior to IM IFNβ-1a injection and 4–6 hours, 8–10 hours, and 12–15 hours after injection. During each clinic visit, subjects were to remain in the clinic at least until after the administration of the last dose of acetaminophen and the last FLS assessment (12–15 hours post-injection). In general, subjects remained in the clinic for 24 hours post-injection.

Assessments

The primary study endpoint was the mean relative change in FLS severity from pre-injection to 4–6 hours post-injection over the 8-week study period. Secondary study endpoints included mean change in FLS assessments at 12–15 hours post-injection and FLS incidence (≥2-point increase in total FLS severity score over the pre-injection score) at the 4–6-hour and 12–15-hour post-injection time points over 8 weeks.

At each weekly clinic visit, FLS were assessed during the 1-hour period preceding IM IFNβ-1a injection and at 4–6 hours and 12–15 hours post-injection, with each assessment performed immediately after acetaminophen administration. At each of these time points, the individual FLS of muscle aches, chills, and fatigue were each rated on a 4-point scale (0 = absent; 1 = mild, does not interfere with daily activities; 2 = moderate, sufficient to interfere with daily activities; 3 = severe, bed rest required; Table 1). Fever (body temperature) was also measured and rated on a 4-point scale as shown in Table 1 at pre-injection and post-injection time points. A total FLS severity score, ranging from 0 to 12, was calculated based on the summation of the four individual symptom and fever scores. Consistent with the approach taken by previous investigators[5], a change in total score of ≥2 points

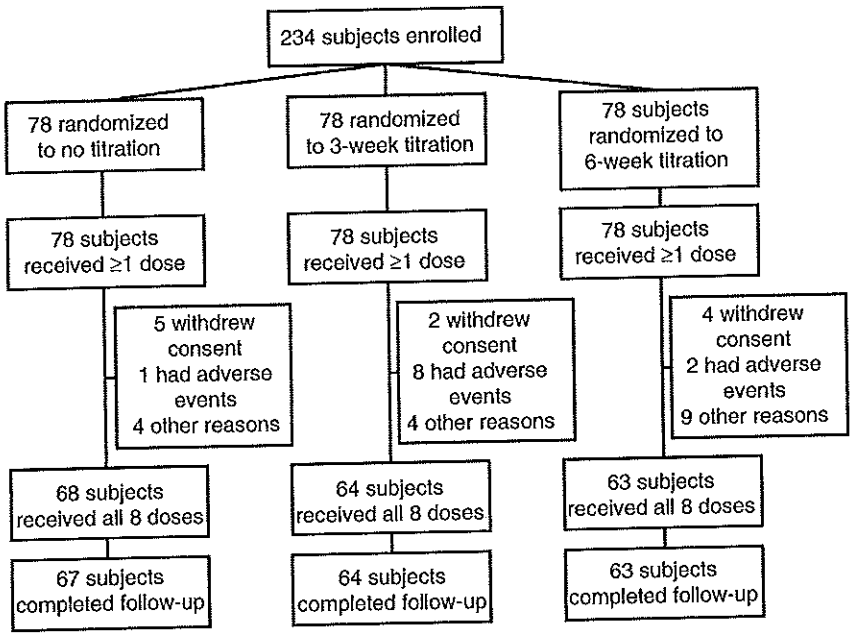

Figure 2. Subject disposition.

above the pre-injection score was pre-specified as positive for the presence of FLS.

Safety and tolerability were assessed throughout the 8-week treatment period and during a 2-week follow-up period after the last IM IFNβ-1a injection. Specific assessments included the incidence and types of adverse events (AEs), standard laboratory test measures, vital signs, 12-lead electrocardiogram measures, and physical examination.

Statistical analyses

Analysis methods

For FLS severity, total score change from baseline (pre-injection) was analyzed using a linear mixed model, which takes into account the dependence among repeated measures within each subject, to test for overall treatment differences over the treatment period. FLS incidence was defined as the proportion of subjects experiencing a post-dose change in FLS score of $\geq$2 points from pre-injection. The generalized estimating equation (GEE) method was used to analyze the incidence of FLS over the treatment period, which was also adjusted for repeated measurements. Logistic regression was used to compare the incidence of FLS during the pre-defined periods of weeks 1–4 and weeks 5–8. Missing values were imputed using the last observation carried forward (LOCF) method. Safety data were analyzed using summary statistics.

Sample size

The original sample size required for this study was estimated to be 120 subjects in order to obtain 108 evaluable subjects, assuming a 10% dropout rate. This sample size calculation was based on the assumption that the effect of each titration scheme on FLS was similar to that reported in an earlier study[5]. However, during the initial weeks of the study, a blinded review suggested that the incidence of FLS was much lower than expected. Therefore, an examination of blinded aggregate interim data was performed on results from the first 4 weeks of the study. Based on evaluation of the blinded interim study data, a sample size of 198 (66 subjects per arm) would provide approximately 90% power to detect a 70% reduction in FLS between the titration and no-titration arms using a stratified t test at a two-sided significance level of 0.05. FLS analyses included data from randomized subjects receiving $\geq$1 dose of study treatment.

Results

Subjects

A total of 234 subjects were enrolled in the study, with 78 subjects randomized to each of the three IM IFNβ-1a treatment groups (Figure 2). Of these 234 subjects, 194 (83%) completed the study. The most frequent reasons for study discontinuation were withdrawal of consent (5%) and treatment-emergent AEs (5%).

Baseline demographics for all 234 subjects are presented in Table 2. Age and gender distribution in these healthy volunteers was similar to the general population characteristics of patients with MS[14]; the majority of study subjects (62%) were female and the mean age was

Table 2. Baseline demographics.

	No titration	3-week titration	6-week titration	Total
n	78	78	78	234
Mean age, years (SD)	32.1 (9.74)	31.8 (9.60)	34.7 (10.82)	32.9 (10.11)
Female (%)	52 (67)	44 (56)	49 (63)	145 (62)
Mean weight (SD)	71.51 (10.383)	70.21 (11.248)	71.98 (11.515)	71.23 (11.037)
Mean BMI (SD)	25.64 (2.779)	24.88 (2.702)	25.78 (2.615)	25.44 (2.717)
White race (%)	67 (86)	67 (86)	63 (81)	197 (84)

BMI, body mass index; SD, standard deviation.

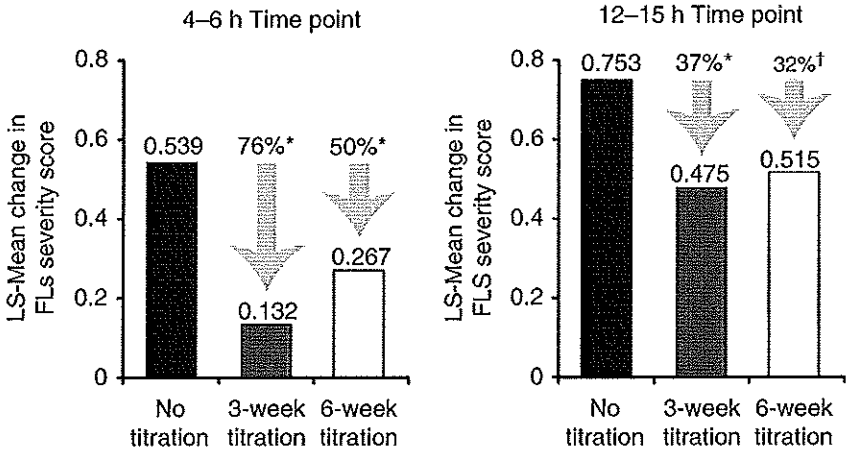

Figure 3. Least squares-mean change in overall FLS severity score from pre-injection to post-injection time points over 8 weeks. LOCF analysis. *Change vs. no titration: $p<0.001$. †Change vs. no titration: $p=0.002$.

32.9 years. Baseline demographics were generally similar across the three treatment groups, although the percentage of females was somewhat lower in the 3-week-titration group (56%) than in the 6-week-titration group (63%) or the no-titration group (67%).

Post-dose FLS severity

The overall change in FLS severity between pre-injection and the 4–6-hour and 12–15-hour post-injection time points over the 8-week treatment period was significantly lower in subjects who received the 3-week ($p<0.001$ for both time points) and 6-week (4–6-hour time point: $p<0.001$; 12–15-hour time point: $p=0.002$) IM IFNβ-1a titration regimens than in those who received the no-titration regimen (Figure 3). At 4–6 hours post-injection, the least squares (LS)-mean change in FLS was 0.539 with no titration, 0.132 with 3-week titration (76% reduction vs no titration; $p<0.001$; primary endpoint), and 0.267 with 6-week titration (50% reduction vs no titration; $p<0.001$). Titration-associated reductions in FLS severity were also observed 12–15 hours post-injection, with LS-mean changes in FLS at this time point of 0.753 with no titration, 0.475 with 3-week titration (37% reduction; $p<0.001$), and 0.515 with 6-week titration (32% reduction; $p=0.002$).

Post-dose FLS incidence

Over 8 weeks, FLS incidence was significantly lower in the 3-week (4–6-hour time point: $p<0.001$; 12–15-hour time point: $p=0.006$) and 6-week (4–6-hour time point: $p=0.023$; 12–15-hour time point: $p=0.027$) IM IFNβ-1a titration groups than in the no-titration group (Table 3). The significantly lower incidence of FLS at 4–6 hours post-injection in the 3-week-titration group compared with the no-titration group persisted over weeks 1–4 (9% vs 28%; $p=0.003$) and weeks 5–8 (6% vs 19%; $p=0.022$). The relative reduction in FLS incidence at 12–15 hours post-injection with 3-week titration versus no titration was also significant during weeks 1–4 (27% vs 50%; $p=0.001$), but no significant difference was noted during weeks 5–8 (26% vs 29%; $p=0.584$). Additional analysis of the mean change in FLS scores from pre-injection to 4–6 hours post-injection by titration regimen showed that the consistent reductions in FLS scores observed with fast titration were not offset by worse FLS scores once the full dose was achieved (Figure 4).

Safety and tolerability

Each IM IFNβ-1a regimen (3-week titration, 6-week titration, and no titration) was well tolerated, with a safety profile consistent with the current IM IFNβ-1a package labeling. The overall incidence of treatment-emergent AEs was slightly lower in both titration groups than in the no-titration group, although the types of reported AEs were generally similar across the three treatment groups (Table 4). The most frequently reported AEs were headache, myalgia, pyrexia, chills, fatigue, body temperature increase, injection site pain, and nausea. There were no deaths or serious adverse events reported in this study. AEs led to the withdrawal of one subject (1%) in the no-titration group, nine subjects (11.5%) in the 3-week-titration group, and two subjects (2.6%) in the 6-week-titration group. The only AE resulting in the withdrawal of more than one subject was upper respiratory tract infection (four subjects in the 3-week-titration group and one subject in the 6-week-titration group). No clinically significant changes or treatment-group differences were observed in laboratory test results, vital signs, 12-lead electrocardiogram findings, or physical examination findings.

Table 3. Odds ratio[a] of FLS.

Post-injection time point	3-week titration ($n=78$)	6-week titration ($n=78$)
4–6 hours		
OR (95% CI)	0.179 (0.075, 0.429)	0.414 (0.194, 0.884)
p value	<0.001	0.023
12–15 hours		
OR (95% CI)	0.469 (0.272, 0.807)	0.562 (0.338, 0.936)
p value	0.006	0.027

[a]Defined as the proportion of subjects who experience FLS (post-dose change over pre-injection of ≥2 points).
LOCF analysis. Data calculated using the generalized estimating equations method, analyzing the overall treatment difference on the repeated measures over 8 weeks. OR estimated using the no-titration group as the control method.
FLS, flu-like symptoms; OR, odds ratio; CI, confidence interval.

Discussion

This is the first randomized, dose-blinded, controlled study to characterize the effect of dose titration on the severity and incidence of IFNβ-related FLS during treatment initiation. In this study, titration of once-weekly IM INFβ-1a (30 μg) in quarter-dose increments over either 3 weeks or 6 weeks resulted in a clinically significant reduction in the severity and incidence of FLS compared with administration of the drug without titration. Importantly, the consistent reductions in FLS scores observed with 3-week titration were not offset by worse FLS scores once the full dose was achieved; in other words, with 3-week titration, the mean change in FLS score remained below that of the no-titration group throughout the entire observation period. This result suggests that the current findings are likely to be driven by a true reduction in FLS associated with titration that is maintained over time, rather than a postponement in the occurrence of FLS. Flu-like symptoms are generally worse during treatment initiation and attenuate over time in patients initiated on interferon beta-1a therapy[3,5]; thus, patients may benefit most from reduced FLS during the early weeks of therapy, as was achieved in the present study following both 3-week and 6-week dose titration. The diminishing difference in FLS severity between subjects who received 6-week titrated dosing and those who did not does not undermine the attractiveness of a treatment approach that reduces early FLS. Both IM IFNβ-1a dose-titration regimens were well tolerated, with safety profiles that are consistent with the

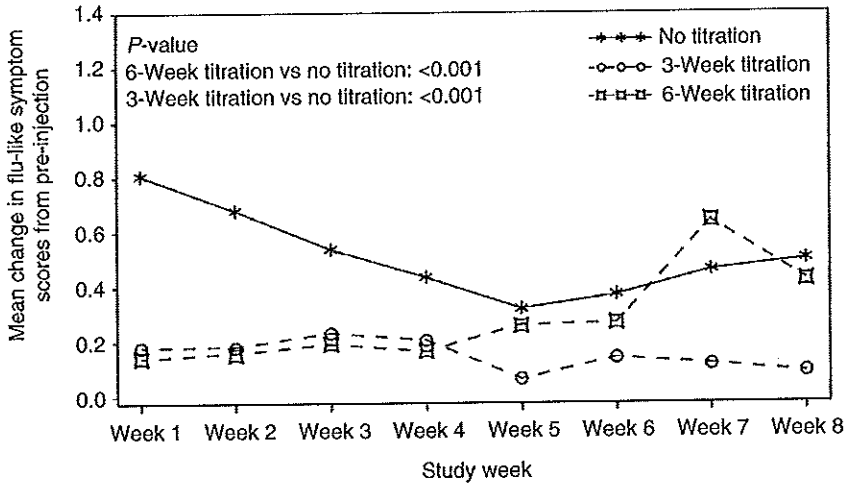

Figure 4. Mean change in flu-like symptom scores from pre-injection to 4–6 hours post-injection by titration regimen.

known safety profile of IM IFNβ-1a. Taken together, these results provide support for using dose titration in clinical practice to reduce the severity and incidence of FLS during initiation of IM IFNβ-1a therapy.

All subjects enrolled in this study received prophylactic acetaminophen. NSAIDs or acetaminophen are routinely administered in clinical practice to reduce the severity and incidence of IFNβ-related FLS. Acetaminophen was selected for use in this study because it is more widely available. Since subjects in all three randomization arms received acetaminophen at the specified time points throughout the study, these results suggest that the effects of dose titration on the severity and incidence of FLS during IFNβ-1a treatment initiation may be independent of the effects of acetaminophen.

Our study findings both confirm and broaden the results reported in an open-label study of 47 patients with relapsing-remitting MS who were randomized to receive 12 weeks of IM IFNβ-1a (30 µg) treatment with quarter-dose or half-dose titration in addition to acetaminophen or ibuprofen[5]. In this initial study, the proportion of patients with FLS at the 4–6-hour and 12–15-hour post-injection time points during the 12-week treatment period was lower in both titration groups than in the no-titration group, with significant reduction in post-injection FLS achieved during the first 2 weeks of treatment with quarter-dose titration compared with no titration ($p = 0.015$).

Several study limitations warrant consideration. First, there is currently no validated assessment tool for evaluating the severity of FLS. This study's assessment parameters for fever, muscle aches, chills, and fatigue correspond to symptoms frequently reported as being experienced by patients following initiation of treatment with interferons and were consistent with the assessment endpoints employed in a previous study of FLS in MS patients[5]. Second, our study enrolled healthy volunteers, which could raise concerns about the applicability of our data to FLS in patients initiating IM IFNβ-1a treatment for MS. However, the frequent occurrence of FLS with the use of interferons across several disease states[15–19] strongly suggests that the mechanisms of interferon-associated FLS are not specifically linked to MS; thus, our data in healthy subjects are likely to apply generally. Third, more females were randomized to the 3-week-titration group than to the 6-week-titration and no-titration groups. While it is possible that this slight gender imbalance may have affected the results of the study, a post hoc analysis adjusting for gender was performed and the results showed that gender was not significantly associated with FLS severity at 4–6 hours post-injection. In this regard, it is unlikely that our conclusions regarding the efficacy of titration are confounded by gender effects.

Finally, while the time points used in the study (4–6 hours and 12–15 hours post-injection) were selected to allow for assessment of the early and later effects of IM IFNβ-1a titration on post-injection FLS, we acknowledge that the protocol did not support an assessment of the impact of titration on symptoms occurring substantially later after injection. It is important to note that no conclusions can be drawn from this study regarding potential differences in the efficacy of IM IFNβ-1a due to titration schedules. A titration schedule may have an effect on treatment efficacy. Nevertheless, the consistency of our findings across the time points studied provides evidence of a clinically meaningful beneficial effect of titration, even if such effects are attenuated at later time points.

Table 4. Adverse events occurring in ≥5% of subjects in any group.

n (%)	No titration (*n* = 78)	3-week titration (*n* = 78)	6-week titration (*n* = 78)	Total (*n* = 234)
Any AE	78 (100)	74 (95)	73 (94)	225 (96)
Headache	56 (72)	52 (67)	49 (63)	157 (67)
Myalgia	58 (74)	46 (59)	49 (63)	153 (65)
Pyrexia	38 (49)	37 (47)	36 (46)	111 (47)
Chills	38 (49)	33 (42)	33 (42)	104 (44)
Fatigue	40 (51)	31 (40)	28 (36)	99 (42)
Body temperature increased	26 (33)	23 (29)	27 (35)	76 (32)
Injection site pain	21 (27)	14 (18)	17 (22)	52 (22)
Nausea	12 (15)	12 (15)	11 (14)	35 (15)
Tachycardia	11 (14)	8 (10)	3 (4)	22 (9)
Injection site erythema	4 (5)	5 (6)	9 (12)	18 (8)
Somnolence	5 (6)	10 (13)	3 (4)	18 (8)
Vomiting	4 (5)	7 (9)	6 (8)	17 (7)
Dizziness	5 (6)	6 (8)	5 (6)	16 (7)
Oropharyngeal pain	6 (8)	3 (4)	3 (4)	12 (5)
Heart rate increased	8 (10)	0	2 (3)	10 (4)
Muscle spasms	5 (6)	2 (3)	3 (4)	10 (4)
Nasal congestion	3 (4)	3 (4)	4 (5)	10 (4)
Oral herpes	3 (4)	3 (4)	4 (5)	10 (4)
Dyspepsia	2 (3)	2 (3)	4 (5)	9 (4)
Injection site hemorrhage	6 (8)	3 (4)	0	9 (4)
Upper respiratory tract infection	2 (3)	4 (5)	2 (3)	8 (3)
Abdominal pain	1 (1)	5 (6)	1 (1)	7 (3)
Cough	1 (1)	1 (1)	5 (6)	7 (3)
Diarrhea	1 (1)	4 (5)	2 (3)	7 (3)
Feeling cold	4 (5)	1 (1)	1 (1)	6 (3)
Paresthesia	4 (5)	1 (1)	0	5 (2)

Conclusion

This study clearly demonstrated that titration in quarter-dose increments over 3 weeks or 6 weeks reduces the severity and incidence of FLS in patients initiating IM IFNβ-1a.

Transparency

Declaration of funding
This study was supported by Biogen Idec Inc.

Declaration of financial/other relationships
M.A.M. has disclosed that he has no significant relationships with or financial interests in any commercial companies related to this study or article. T.R.Z., D.T., Y.T., and A.D. are employees of Biogen Idec.

Acknowledgements
Medical writing assistance was provided by Tracy Wetter, PhD, and Matthew Jacobson of Infusion Communications and was funded by Biogen Idec Inc.

Data were previously presented in poster format at the Consortium of Multiple Sclerosis Centers 2011 Annual Meeting held on 1–4 June in Montreal, Canada. They were also be presented in poster format at the European Federation of Neurological Societies 2011 Annual Meeting on 10–13 September in Budapest, Hungary, and at the European Committee for Treatment and Research in Multiple Sclerosis 2011 Annual Meeting on 19–22 October in Amsterdam, The Netherlands.

References

1. Moses Jr H, Brandes DW. Managing adverse effects of disease-modifying agents used for treatment of multiple sclerosis. Curr Med Res Opin 2008;24:2679-90
2. Girouard N, Théorêt G. Management strategies for improving the tolerability of interferons in the treatment of multiple sclerosis. Can J Neurosci Nurs 2008;30:18-25
3. Bayas A, Rieckmann P. Managing the adverse effects of interferon-β therapy in multiple sclerosis. Drug Safety 2000;22:149-59
4. Frohman E, Phillips T, Kokel K, et al. Disease-modifying therapy in multiple sclerosis: strategies for optimizing management. Neurologist 2002;8: 227-36
5. Brandes D, Bigley K, Hornstein W, et al. Alleviating flu-like symptoms with dose titration and analgesics in MS patients on intramuscular interferon beta-1a therapy: a pilot study. Curr Med Res Opin 2007;23:1667-72
6. Wroe SJ. Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis. J Int Med Res 2005;33:309-18
7. Pelletier J. Open-Label, randomised, parallel group study of Rebif 44 mcg administered 3 times weekly with or without initial titration in relapsing-remitting multiple sclerosis patients previously treated with low-dose interferon beta therapy. Presented at European Committee for Treatment and Research in Multiple Sclerosis 21st Congress; 28 September–1 October 2005; Thessaloniki, Greece. Poster 302
8. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996; 39:285-94
9. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a initiated during a first demyelinating event in multiple sclerosis. N Engl J Med 2000;343:898-904
10. Kinkel RP, Kollman C, O'Connor P, et al. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. Neurology 2006;66:678-84
11. Panitch H, Goodin DS, Francis G, et al. Randomized, comparative study of interferon β-1a treatment regimens in MS. The EVIDENCE Trial. Neurology 2002;59:1496-506
12. Durelli L, Verdun E, Barbero P, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet 2002;359:1453-60
13. Avonex [prescribing information]; Cambridge, MA, USA: Biogen Idec Inc., 2008
14. Who gets MS? National MS Society. New York: National Multiple Sclerosis Society, 2011. Available at: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/who-gets-ms/index.aspx [Last accessed 14 July 2011]
15. Clarke J. Mechanisms of adverse drug reactions to biologics. In: Hofmann FB, Ganten D, Page CP Handbook of Experimental Pharmacology. Berlin and New York: Springer-Verlag, 2010. Vol. 196, part 3, 453-74
16. Margolis K, Nichol KL, Poland GE, et al. Frequency of adverse reactions after influenza vaccination. Am J Med 1990;88:27-30
17. Nadjar Y, Coutelas E, Prouteau P, et al. Injection of interferon-beta in the morning decreases flu-like syndrome in many patients with multiple sclerosis. Clin Neurol Neurosurg 2011;113:316-22
18. Ali A, Owayed S, Al-Qabandi W, et al. Pegylated interferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C genotype 4 in adolescents. Ann Hepatol 2010;9:156-60
19. Jara P, Hierro L, de al Vega A, et al. Efficacy and safety of peginterferon-α2b and ribavirin combination therapy in children with chronic hepatitis C infection. Pediatr Infect Dis J 2008;27:142-8

Phillips et al. BMC Neurology 2011, 11:126
http://www.biomedcentral.com/1471-2377/11/126

BMC Neurology

RESEARCH ARTICLE Open Access

An open-label, multicenter study to evaluate the safe and effective use of the single-use autoinjector with an Avonex® prefilled syringe in multiple sclerosis subjects

J Theodore Phillips[1], Edward Fox[2], William Grainger[3], Dianne Tuccillo[4], Shifang Liu[4] and Aaron Deykin[4*]

Abstract

Background: The ability to self-inject in patients with multiple sclerosis (MS) has been associated with a reduced risk of missed injections and drug discontinuation, and a beneficial effect on patients' independence. However, injection anxiety, needle phobia and disease-related disability are major barriers to a patient's ability to self-administer treatment. Use of an autoinjector may improve patients' ability to self-inject. This study evaluated the safe and effective use of Avonex Pen™ (prefilled pen), a single use autoinjector, for intramuscular delivery of interferon beta-1a (IM IFNβ-1a, Avonex) in MS patients.

Methods: This was a Phase IIIb, open-label, single-country, multicenter trial in MS patients currently using IM IFNβ-1a prefilled syringes. Patients received weekly 30 mcg IM IFNβ-1a treatment over 4 weeks. On Day 1, patients self-administered IM IFNβ-1a using a prefilled syringe at the clinic. On Day 8, patients received training on the prefilled pen and self-administered IM IFNβ-1a using the device. On Day 15, patients self-administered IM IFNβ-1a at home using the prefilled pen. A final injection occurred at the clinic on Day 22 when patients self-administered IM IFNβ-1a using the prefilled pen while clinic staff observed and completed a detailed questionnaire documenting patients' ability to self-inject with the device. Serum neopterin levels were evaluated pre and post-injection on Days 1 and 8. Adverse events were monitored throughout.

Results: Seventy-one (96%) patients completed the study. The overall success rate in safely and effectively using the prefilled pen was 89%. No device malfunctions occurred. One unsuccessful administration occurred at Day 22 due to patient error; no patient injury resulted. Patients gave the prefilled pen high ratings (8.7-9.3) on a 10-point scale for ease of use (0 = extremely difficult, 10 = extremely easy). Ninety-four percent of patients preferred the prefilled pen over the prefilled syringe. Induction of serum neopterin levels, serving as a biomarker for type 1 interferon action, was similar to that of the prefilled syringe. The prefilled pen demonstrated a safety profile comparable to the prefilled syringe.

Conclusions: The prefilled pen is a safe and effective device for administration of IM IFNβ-1a and represents an alternative method for self-injection for MS patients using this therapy.

Trial registration: This study is registered at clinicaltrials.gov, identifier: NCT00828204

* Correspondence: aaron.deykin@biogenidec.com
[4]Biogen Idec Inc., 14 Cambridge Center, Cambridge, Massachusetts, USA
Full list of author information is available at the end of the article

Background

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that can lead to extensive neurodegeneration and subsequent irreversible disability. Symptoms of MS affect motor, sensory, visual, and autonomic systems but are not limited to these areas alone [1]. While there is no cure for MS, treatment with disease modifying therapies (DMTs) can reduce the frequency of relapses and disability associated with the disease [2-5].

For patients prescribed injectable DMTs, self-administration has been associated with a reduced risk of missed injections and drug discontinuation, and a beneficial effect on patients' sense of independence [6-8]. However, patients with MS face a variety of challenges that limit their ability to self-administer treatment [9]. Injection anxiety, including anticipation of pain, fear of hitting bone, inability to complete the injection effectively and fear of needle breakage, is an important barrier to self-injection [10]. Needle phobia, a component of injection anxiety, occurs in approximately 50% of patients with MS and therefore presents a significant concern for patients using injectable therapies [11]. Furthermore, as MS is a disease that affects the CNS, additional challenges to self-injection develop as the disease progresses and disability accumulates. Impairment of fine motor skills and decreased coordination present obstacles to the independent use of self-injected MS therapies [12].

The clinical importance of enabling self-injection is supported by various studies that have shown that the injection process can be made easier for patients through the use of automated injectors [13-16]. Autoinjectors have been shown to improve treatment adherence, reduce injection related adverse events (AEs) such as pain, and decrease injection anxiety [17-19]. Given these clinical benefits and recognizing the frequency at which barriers to self-injection are encountered by MS patients, including those using intramuscular interferon beta-1a (IM IFNβ-1a, Avonex) [11,20], it is evident that a mechanism to facilitate a patient's ability to self-inject IM IFNβ-1a is needed.

The Avonex Pen™ (prefilled pen) is a single use autoinjector containing the commercially available Avonex® Prefilled Syringe for once-weekly intramuscular (IM) injection. The prefilled pen has been developed as the first IM autoinjector available for long-term treatment with IM IFNβ-1a. Features of the prefilled pen have been specifically designed to overcome the barriers to self-injection and facilitate the technical aspects of the injection process. These features include a protective sheath that conceals the needle within the device prior to injection, automated needle insertion and medication dispensing, a diameter and length designed to stabilize the device during the injection process, a safety mechanism which prevents accidental injection, and a visual indicator to confirm the full dose has been administered.

The prefilled pen has the potential to improve injection methods and simplify the self-injection process, thereby addressing an unmet need in patients using IM IFNβ-1a. This study was conducted to evaluate the safe and effective use of the prefilled pen for IM delivery of IFNβ-1a in patients with MS.

Methods

Study Design

This was a Phase IIIb, open-label, single-arm, multicenter study to evaluate the safe and effective use of the prefilled pen. A total of 17 sites in the United States participated. Investigators at each site obtained institutional review board (IRB) approval for the study protocol. This study was performed in accordance with all international, federal and local regulations, and written informed consent was obtained from each patient prior to eligibility evaluations. Study duration was 6 weeks, including a 14-day screening period and a 4 week IM IFNβ-1a treatment period. There were a total of 9 scheduled clinic visits per patient.

Study Population

Study participants were 18 to 65 years of age. Eligibility criteria required patients to have been self-administering the prefilled syringes to treat MS for the 12 weeks prior to the screening visit. Key exclusion criteria included concomitant treatment with prescribed immunomodulators or immunosuppressants, and unwillingness or inability to comply with the requirements of the protocol, including the presence of any condition (physical, mental, or social) that was likely to affect a patient's ability to return for follow up visits on schedule.

Device Description

The prefilled pen is shown in Figure 1. This device uses two springs to deliver the IM IFNβ-1a dose. The first spring performs the needle insertion and the second spring dispenses the medication. Activation of the second spring is dependent upon the successful completion of the first spring's activity. The prefilled pen is 13.5 cm in length and has a diameter of 1.5 cm. A 25 G × 5/8 inch (16 mm) needle, housed in a protective shield within the device, is used to deliver the IM IFNβ-1a dose.

For the manual injection with the prefilled syringe (Injection 1), patients used their own supply of IM IFNβ-1a prefilled syringes. The needle size used for Injection 1 was not recorded for each patient since the

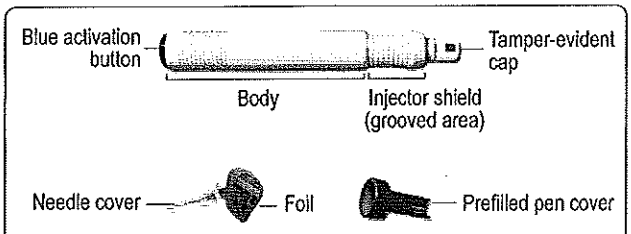

Figure 1 Avonex Pen.

needle size used for manual injection of the prefilled syringe can vary between patients. A 23 G × 1.25 inch (32 mm) needle is included in the commercially available IM IFNβ-1a prefilled syringe package, however a different needle size (25 G × 1 inch) is also approved for use with the IM IFNβ-1a prefilled syringe. The decision of which needle a patient should use is based on the needs of the patient and left to the discretion of the prescribing physician, per IM IFNβ-1a prescribing information.

Treatment

All patients received 30 mcg doses of IM IFNβ-1a once weekly over 4 weeks. Patients who were taking prophylactic therapy for flu-like symptoms at the start of the study continued the same medication and dose until their participation in the study was completed. If MS relapses occurred during the study, these were treated at the Investigator's discretion following standard medical practice, as long as treatment did not involve any of the protocol excluded concomitant medications. Treatment for spasticity, fatigue, or other MS associated symptoms was not restricted.

Treatment Schedule

Patients who met the eligibility criteria during the 14-day screening period entered into a 4-week IM IFNβ-1a treatment period. Injection 1 took place on Day 1 and was administered at the study clinic by the patient using a prefilled syringe from their own supply of IM IFNβ-1a prefilled syringes and needles as prescribed by their physician.

Injection 2 occurred on Day 8 and was administered at the study clinic by the patient using the prefilled pen following training provided by the clinic site Trainer/Observer. During this injection, the Trainer/Observer observed patient use of the prefilled pen and reinforced training as needed. Injection 3 occurred on Day 15 and was self-administered by the patient at home using the prefilled pen. The final injection, Injection 4, occurred on Day 22 and was administered at the study clinic by the patient using the prefilled pen. At this clinic visit the Trainer/Observer observed patient use of the prefilled pen and completed a detailed questionnaire documenting patients' ability to self-inject with the device. The Trainer/Observer completed the observation in a hands off manner; no assistance or correction was provided to the patient during this final injection. In total, patients were to receive one injection with the prefilled syringe and three injections with the prefilled pen.

Evaluations were made at various time points throughout the study. The treatment schedule and corresponding evaluations are displayed in Table 1.

Study Endpoints

Primary

The primary assessment of the safe and effective use of the prefilled pen was to evaluate the overall success rate as measured by the proportion of patients who successfully used the device. Data for determining the overall success rate were generated from an observation form that was completed by the Trainer/Observer during the final injection (Day 22). The observation form was composed of a series of questions organized around the three key steps of the injection process: device setup, self-administration of injection, and capping and disposal of the device. All actions captured in the observation form that would define the patient's handling of the prefilled pen as a failure were pre-defined in the protocol. Failure was further categorized as "failure patient induced" or "failure-possible device malfunction." Overall success was defined as no failures occurring during the patient's use of the device.

Additional

Additional endpoints in this study included patient assessments, clinician assessments, a pharmacodynamic evaluation, and safety monitoring.

Patient Preference Assessment A preference questionnaire was administered to the patients on the last clinic visit (either Day 23 or the final visit if patient was withdrawing early from the study). The questionnaire investigated whether patients preferred the prefilled pen or the prefilled syringe, and scored patient preference for specific features of the prefilled pen compared to the prefilled syringe using a grading scale ranging from 0 (defined on the form as "much worse") to 10 (defined on the form as "much better"); definitions for integers 2-9 on the scale were not specified.

Patient Assessment of Injection Procedure The injection procedure was assessed by each patient in order to evaluate whether patients experienced any difficulty with the processes of preparing, injecting, removing, and disposing after each of the 4 injections (Days 1, 8, 15, 22).

Patient Assessment of Injection Site Pain Injection site pain was evaluated pre and post injection by patients for each of the 4 injections (Days 1, 8, 15, 22). Pain was evaluated on a scale from 0 (no pain) to 10 (extremely painful).

Table 1 Treatment period and evaluation schedule

	Screening visit	Injection using the prefilled syringe					Injections using the prefilled pen			EOS or EW
	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Home	Clinic	Clinic
	14-day period	Day 1	Day 2	Day 3	Day 8	Day 9	Day 10	Day 15	Day 22	Day 23
Treatment and evaluations		Injection 1			Injection 2			Injection 3	Injection 4	
Study enrollment		x								
Injection using the prefilled syringe		x								
Neopterin serum sample collection		x[a]	x[b]	x[c]	x[a]	x[b]	x[c]			
Prefilled pen training					x					
Injection using the prefilled pen					x			x	x	
Patient assessment of the prefilled pen training materials					x			x	x	
Patient assessment of injection site pain		x[d]			x[d]			x[d]	x[d]	
Patient assessment of ease of use		x			x			x	x	
Patient assessment of injection procedure		x			x			x	x	
Clinician assessment of injection site		x[e]	x		x[e]	x			x[e]	x
Observation form									x	
Preference questionnaire										x
Patient assessment and dosing information forms dispensed					x					
Concomitant therapy and adverse events		Monitor and record throughout study								

EOS, end of study; EW, early withdrawal.

[a]Neopterin samples were to be obtained 1 hour pre-injection.

[b]Neopterin serum samples were to be obtained 24 hours ± 2 hours post-injection.

[c]Neopterin serum samples were to be obtained 48 hours ± 2 hours post-injection.

[d]To be completed within 1 hour before injection and also immediately after injection.

[e]Clinician injection site assessment was to be performed within 1 hour before injection.

Patient Assessment of Ease of Use Patients evaluated the "ease of use" for each of the 4 injections performed (Days 1, 8, 15, 22) by using the Ease-of-Use Grading Scale to indicate how easy it was for the patient to perform the injection. The scale ranged from 0 (extremely difficult) to 10 (extremely easy).

Patient Assessment of Training Materials For each use of the prefilled pen (Days 8, 15, 22), patients evaluated how easy or difficult it was to read and understand the training materials.

Clinician Injection Site Assessment Clinicians at the study site assessed injection sites 1 hour before injection and 24 hours following injection for each administration that took place at the clinic (Days 1, 8, 22). The injection site was examined for erythema, induration, temperature, and tenderness.

Pharmacodynamics In order to evaluate levels of neopterin, a well-established biological marker of pharmacodynamic response to activation of the Type 1 interferon receptor, blood samples were collected from patients one hour prior to injection and 24 and 48 hours following injection for Injection 1 (Day 1, prefilled syringe) and Injection 2 (Day 8, prefilled pen).

Safety Adverse events were monitored throughout the study.

Statistical Analyses

A 10% dropout rate was assumed for this study. A sample size of 70 patients was required to provide a 95% confidence interval of the success rate [82.6%, 97.4%] based on the assumption that 90% of patients would successfully use the prefilled pen. The population used to evaluate the primary outcome consisted of those patients who received Injection 1 with the prefilled syringe, received at least one injection with the prefilled pen, and had a completed observation form.

Summary and descriptive statistics were used in this study. No formal statistical testing was preplanned in the protocol.

Results

Patient demographics

Of the 74 enrolled patients, 64 (86%) were female. Mean patient age was 49.6 years (range: 22 to 65 years). The mean body mass index (BMI) of the study population was 28.92 kg/m^2 (range: 17.9 to 42.2 kg/m^2).

Patient Exposure to Study Treatment

Of 74 enrolled patients, 71 patients (96%) completed the study. All 74 enrolled patients received a self-injection using the prefilled syringe. Two patients discontinued from the study following the injection with the prefilled syringe prior to receiving an injection with the prefilled pen (one patient was withdrawn after missing two clinic visits and the other patient was withdrawn due to a MS relapse). Seventy two patients received at least one self-injection with the prefilled pen and 71 patients completed all three injections with the device. One patient completed the final injection but did not have a completed observation form. As a result, the observation form was only completed for 70 patients. In total, 215 injections were administered with the prefilled pen.

Overall Success Rate

The overall injection success rate was 89% (62/70 patients). No failures due to device malfunction and no damaged or bent needles were reported. Eight (11%) patient induced failures occurred, the majority of which took place during device setup (seven patients removed the needle cap manually rather than by extending the injector shield). None of these events resulted in patient injury and all patients were able to complete administration with the prefilled pen. Patient-induced failures resulting in the device becoming unusable occurred in one patient. In this case the patient did not follow instructions and removed the device from the thigh prematurely before medication was administered; upon a second attempt the patient was able to successfully complete all steps of the injection process. Patient success at each observation of self-administration using the prefilled pen is described in Table 2.

Patient Preference Assessment

The majority (94%) of patients indicated a preference for the prefilled pen over the prefilled syringe. Patients evaluated the prefilled pen in comparison to the prefilled syringe using a grading scale ranging from 0 (much worse) to 10 (much better). Across all domains, patient preference for the prefilled pen was strong (Figure 2). Patient preference was related to key features of the injection process, including ease of holding and gripping (mean score of 8.7), ease of injection (mean score of 9.2), level of pain (mean score of 8.3), level of independence (mean score of 8.5), level of confidence (mean score of 8.7), and needle anxiety (mean score of 9.0). The most common reasons for patient preference for the prefilled pen are listed in Figure 3.

Patient Assessment of Injection Site Pain

Following injection with the prefilled syringe, the mean pain score was low, 1.7 (out of 10). The mean pain score for each of the 3 injections with the prefilled pen was also low: 1.0, 1.3, and 0.7 for injections on Days 8, 15, and 22, respectively.

Patient Assessment of Injection Procedure

Eighty-nine percent of patients reported having no difficulty with administration using the prefilled syringe. For

Table 2 Patient success at each self-administration step using the prefilled pen (analysis population, n = 70)

Steps in self-administration using the prefilled pen	Patients who completed step correctly and in an optional manner, *n* (%)
Device setup	
Holds device in an upright position and removes tamper-evident cap	66 (94)
Holds device in an upright position and attaches needle	58 (83)
Extends injector shield all the way, while pointing device away from body	61 (87)
Injection	
Places and holds prefilled pen perpendicularly to anterior lateral thigh (injection site)	68 (97)
Applies firm downward pressure on the body of the prefilled pen and releases the safety lock and fires device by depressing blue activation button	65 (93)
Holds device for a count of 10 seconds before removing needle from thigh	67 (96)
Lifts device straight out, perpendicular to thigh	68 (97)
Visually confirms delivery via circular display window	58 (83)
Capping and disposal	
Caps the device with blue cover	66 (94)
Does not hold blue cover in place while capping prefilled pen	63 (90)

Note: All data were captured in the observation form.

each of the injections using the prefilled pen, 90% of patients reported having no difficulty.

Patient Assessment of Ease of Use

The mean ease of use score for the injection administered with the prefilled syringe was 8.1 (out of 10). For each administration with the prefilled pen, the mean ease of use score was as follows: 8.9 on Day 8, 8.7 on Day 15, and 9.3 for the final injection with the prefilled pen.

Patient Assessment of Training Materials

Patients referred to the written instructions and DVD less with each subsequent injection using the prefilled pen. Of the patients who used the written instructions and DVD, the majority rated them as "very effective" in educating on how to use the prefilled pen (90%-93% for written instructions; 88%-90% for DVD instructions).

Clinician Injection Site Assessment

Clinical injection site assessments made before and after injection were similar between the prefilled syringe and the prefilled pen. For the majority of patients, the clinician found no presence of induration, no temperature variation, and no tenderness at the site following injection with the prefilled syringe or the prefilled pen. Mild erythema was reported in 26% of patients after using the prefilled syringe and in 25% and 23% of patients on Days 8 and 22 after using the prefilled pen. Mild induration and mild tenderness were reported in less than 8% of patients following injections with both the prefilled syringe and the prefilled pen. There were no severe reports of erythema, induration, tenderness and temperature following any injection.

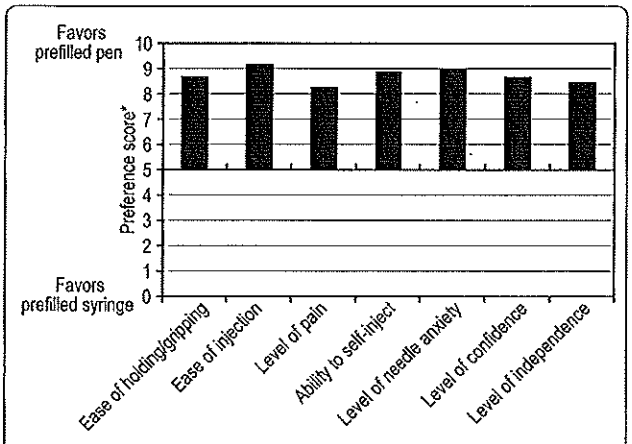

Figure 2 Mean patient preference scores for prefilled pen vs. the prefilled syringe on 7 domains relevant to self-injection (analysis population, n = 70). *Scores in each domain range from 0 (prefilled pen much worse) to 10 (prefilled pen much better).

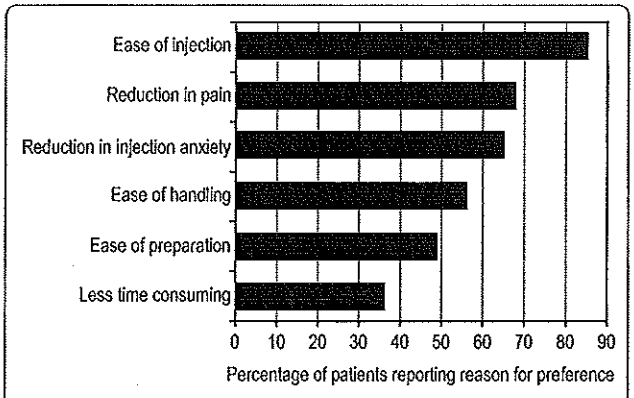

Figure 3 Most common reasons reported for preferring the prefilled pen (analysis population, n = 70).

Pharmacodynamics

Similar increases in mean neopterin serum levels were observed over time following administration with the prefilled pen (6.2 ng/ml before injection, 12.6 ng/mL 24 hours after injection, and 13.7 ng/mL 48 hours after injection) as were seen with the injection using the prefilled syringe (5.6 ng/mL before injection, 10.0 ng/mL 24 hours after injection, and 11.0 ng/mL 48 hours after injection). The mean neopterin induction ratios were similar for injection with the prefilled syringe and the prefilled pen (2.149 and 2.514, respectively).

Safety - Adverse Events

All patients who received at least one dose of IM IFNβ-1a using either the prefilled syringe or the prefilled pen were included in the safety population. The overall incidence of AEs in this study was low and rates were similar between the prefilled syringe and the prefilled pen. One patient experienced a MS relapse during the study period. Eleven percent of patients reported an adverse event with use of the prefilled syringe (Day 1), and 17%, 18%, and 4% of patients reported an adverse event with each injection using the prefilled pen (Days 8, 15, and 22). No safety concerns potentially associated with the prefilled pen were observed. The incidence of injection site reactions was low and pain was infrequently reported with the prefilled pen (Table 3).

Discussion

This open-label study evaluated the safe and effective use of the prefilled pen in patients currently self-administering IM IFNβ-1a via the prefilled syringe. These patients represent the population expected to use the prefilled pen and as such, were believed to be well suited to evaluate the prefilled pen.

Safe and effective use of the prefilled pen was assessed from data captured in the observation form completed by the Trainer/Observer. The comprehensive list of questions in the observation form was developed to provide an overall evaluation of the patients' ability to properly self-inject with the device during the final injection using the prefilled pen. There were no device malfunctions and the overall success rate of the prefilled pen was high (89%), demonstrating that it provides a safe and effective alternative method of administering IM IFNβ-1a. Patients also gave high ratings to the related training materials and injection procedure.

Table 3 The most common (≥3%) treatment-emergent prefilled pen injection site-related adverse events

	n	%
Number of patients who received at least 1 injection with prefilled pen	72	100
Injection site-related adverse event		
Injection site pain	5	7
Injection site hematoma	4	6
Injection site erythema	2	3
Injection site hemorrhage	2	3
Injection site induration	2	3

Note: A patient was counted only once within each preferred adverse event term.

The prefilled pen was specifically designed to overcome multiple challenges of self-injection faced by patients with MS. Features designed to reduce injection anxiety include a protective shield that conceals the needle and automated needle insertion and medication dispensing, which reduces the number of steps involved in the dosing process. Safety features include a mechanism to prevent early injection as well as a visual indicator that allows for confirmation of injection process completion. The diameter and length dimensions are designed to help stabilize the device during the injection process so as to improve ease of use for patients with impaired motor coordination. In this study, 94% of patients preferred the prefilled pen over the prefilled syringe. Reasons for patient preference for the prefilled pen were related to ease of holding and gripping, ease of injection, level of pain, and needle anxiety, confirming that the design of the prefilled pen was successful in making the injection process easier. In addition, although the study was not originally designed to compare the prefilled syringe to the prefilled pen, a post hoc paired *t* test was performed to compare the ease of use assessment at Injection 1 (Day 1, with the prefilled syringe) with Injection 4 (Day 22, with the prefilled pen). Results demonstrated that patients found the prefilled pen statistically significantly easier to use after 3 injections compared to the prefilled syringe after at least 12 uses, as required by study entry criteria (mean ease of use scores 8.1 and 9.3, respectively).

Automated injection devices offer a means to potentially reduce injection site pain. In this study, patient assessment of pain was low for the injection with the prefilled syringe (1.7 out of 10), and numerically lower for each of the three injections with the prefilled pen. A post hoc comparison of the pain assessment at Injection 1 (Day 1, with the prefilled syringe) and Injection 4 (Day 22, with the prefilled pen) was performed by paired *t* test and showed that patients experienced statistically significantly less pain with the prefilled pen by the third use than with the prefilled syringe after at least 12 uses, as required by study entry criteria (mean pain scores 1.7 and 0.7, respectively). The incidence of pain through safety monitoring was also low for both methods of administration. Seven percent of patients reported an AE of pain related to use of the prefilled pen and none of the reports were severe. In addition to pain

assessments, the injection site was assessed at multiple time points during the study by the clinician. Mild erythema was observed at a similar frequency following injection with the prefilled syringe and injection with the prefilled pen. The incidence of other injection site reactions such as temperature, induration, and tenderness were infrequent, and rates were similar for the two injection methods.

Importantly, there were no new safety concerns raised in this study. The safety profile observed with the prefilled pen was similar to the known safety profile of IM IFNβ-1a from the prescribing information and post marketing data.

Although IM injections are frequently administered via a manual syringe with a longer needle, the 25 G × 5/8 inch (16 mm) needle was determined to be the appropriate size for use with the prefilled pen. Earlier development of the prefilled pen using a 23 G × 1.25 inch (30 mm) needle indicated that this length was not appropriate for use with the device due to needle bends, which did not occur in this study with use of the shorter needle. The ability of the needle used in this study to deliver an IM injection is supported by published reports indicating that a 5/8 inch needle (16 mm) can be expected to access the IM space in the majority of patients when applied with a manual syringe [21-23]. Considering the compressive effects related to the forceful application of the prefilled pen to the cutaneous tissue, the shorter needle is likely appropriate for general use [22,24].

As discussed earlier, reduction in needle anxiety and injection pain were amongst the subjective benefits specifically sought in the design of the prefilled pen. We note that the shorter needle length of the prefilled pen may, in addition to its other features, contribute to the observed patient preferences for this device over the prefilled syringe. Our observation that neopterin induction was similar following injection with the prefilled syringe and with the prefilled pen further supports that the 25 G × 5/8 inch (16 mm) needle is the appropriate size to effectively deliver the full dose of IM IFNβ-1a with the prefilled pen as designed.

There are limitations to consider when interpreting the results of this study. First, we acknowledge that the questionnaires and assessments used in the study have not been formally validated. However, they were specifically developed to capture information relevant to the robust evaluation of the safety and efficacy of the prefilled pen.

In addition, several features of the study design and population should be emphasized. We enrolled only patients actively interested in the prefilled pen. In this regard, we are not able to speculate on the outcomes of a similar study conducted in patients who were not interested in a self-injection device. Given the nature of the study, it was also impossible to blind patients and study staff regarding injection method. As such, the data derived from the subjective assessments made in this study may partially reflect patients' and clinicians' expectations for the prefilled pen. The partial crossover study design in which patients switched from injections with the prefilled syringe to injections with the prefilled pen (and not from the prefilled pen to the prefilled syringe) does not allow us to exclude an impact of treatment order on our findings. Additionally, patients evaluated the prefilled syringe injection experience only once, whereas they evaluated the prefilled pen injection experience a total of three times. It could be argued that patient responses may have varied when assessing the different methods since there were repeat evaluations for only one of the methods. However, since the patients in the population selected for this study were currently using the prefilled syringe, it is unlikely that the single assessment of the prefilled syringe would have differed significantly if that assessment had been repeated.

While we acknowledge that this study evaluated the prefilled pen in patients currently self-administering IM IFNβ-1a via the prefilled syringe and therefore does not address its suitability in treatment-naïve patients or when utilized by caregivers, the patient preference and ease of use results indicate the prefilled pen would also be an attractive option for use in these populations.

Conclusions

Injection anxiety and physical limitations are major barriers to self-injection for many patients with MS. These barriers may contribute to poor treatment adherence that may result in a reduction in the clinical benefits of MS therapy.

Results from this study support the safe and effective use of the prefilled pen for self-administration of IM IFNβ-1a by patients with MS. Patients preferred the prefilled pen over the prefilled syringe for reasons related to ease of use, injection pain, needle anxiety, and sense of independence. Data from this study demonstrate the potential for the prefilled pen to fulfil an unmet need in patients using IM IFNβ-1a by offering an alternative method for IM delivery that simplifies the injection process. The prefilled pen provides patients the opportunity to gain the clinical benefits of IM IFNβ-1a treatment while improving their ability to independently manage their disease.

Acknowledgements

The authors thank Kimberly Cushing of Biogen Idec for her assistance in writing the manuscript, and Infusion, An InforMed Group Company, for their assistance in developing the graphics.

The authors would also like to thank the lead investigator and staff at each study site: Jeffrey English, MD (MS Center of Atlanta, Atlanta, GA), Warren Felton, III, MD (Virginia Commonwealth University Medical Center, Richmond,

VA), John Foley, MD (Rocky Mountain MS Clinic, Salt Lake City, UT), Lawrence Goldstick, MD (Neurology Specialists, Inc., Dayton, OH), Mark Gudesblatt, MD (Comprehensive Multiple Sclerosis Care Center, Patchogue, NY), Barry Hendin, MD (Phoenix Neurological Associates LTD, Phoenix, AZ), David Hojnacki, MD (Buffalo General Hospital, Buffalo, NY), William Honeycutt, MD (Neurological Associates, P.A., Maitland, FL), DeRen Huang, MD (Neurology & Neuroscience Associates, Inc., Akron, OH), Michael Kaufman, MD (Carolinas Healthcare System Neuroscience & Spine Institute, Charlotte, NC), Kiren Kresa-Reahl, MD (Capitol Neurology, Charleston, WV), Ellen Lathi, MD (Caritas St. Elizabeth's Medical Center, Boston, MA), Howard Rossman, D.O., F.A.C.N. (Michigan Institute for Neurological Disorders, Farmington Hills, MI), James C. Stevens, MD (Fort Wayne Neurological Center, Fort Wayne, IN).
This study was funded by Biogen Idec.

Author details
[1]Texas Neurology, 6301 Gaston Ave, West Tower, #100, Dallas, Texas, USA. [2]MS Clinic of Central Texas, Central Texas Neurology Consultants, PA, 16040 Park Valley Drive, Building B, Suite 100, Round Rock, Texas, USA. [3]Neurological Physicians of Arizona, Clinical Research Advantage, 726 N. Greenfield Road, Suite 110, Gilbert, Arizona, USA. [4]Biogen Idec Inc., 14 Cambridge Center, Cambridge, Massachusetts, USA.

Authors' contributions
All authors contributed to the manuscript and have read and approved the final version. JTP served as the principal investigator and participated in the study design. JTP, EF, and WG served as study site investigators. DT participated in the conduct of the study and data analysis. SL participated in the study design and performed the statistical analysis. AD participated in the data analysis.

Competing interests
JTP has participated in consulting and/or speakers' bureau with Biogen Idec, Genzyme, Novartis, and Teva Neuroscience, and has participated in clinical research with Biogen Idec.
EF has participated in consulting and/or speakers' bureau with Bayer, Biogen Idec, EMD Serono, Genzyme, Opexa, Novartis, Pfizer, and Teva Neuroscience, and has participated in research studies involving Biogen Idec, Eli Lilly, EMD Serono, Genzyme, Ono, Roche, Sanofi Aventis, and Teva Neuroscience.
WG has participated in consulting, speakers' bureaus, and clinical research with Biogen Idec and Teva Neuroscience.
DT, SL, and **AD** are employees of Biogen Idec.

Received: 26 July 2011 Accepted: 14 October 2011
Published: 14 October 2011

References

1. Compston A, Coles A: Multiple sclerosis. *Lancet* 2008, 372:1502-1517.
2. The IFNB Multiple Sclerosis Study Group: Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* 1993, 43:655-661.
3. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Fischer JS, Goodkin DE, Granger CV, Simon JH, *et al*: Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. In *Ann Neurol. Volume 39*. The Multiple Sclerosis Collaborative Research Group (MSCRG); 1996:285-294.
4. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, Myers LW, Panitch HS, Rose JW, Schiffer RB: Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. In *Neurology. Volume 45*. The Copolymer 1 Multiple Sclerosis Study Group; 1995:1268-1276.
5. PRISMS (Prevention of Relapses and Disability by Interferon b-1a Subcutaneously in Multiple Sclerosis) Study Group: Randomised doubleblind placebo-controlled study of interferon b-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998, 352:1498-504, [Erratum, Lancet 1999; 353:678.].
6. Mohr DC, Cox D, Merluzzi N: Self-injection anxiety training: a treatment for patients unable to self-inject injectable medications. *Mult Scler* 2005, 11:182-185.
7. Buhse M: Efficacy of EMLA cream to reduce fear and pain associated with interferon beta-1a injection in patients with multiple sclerosis. *J Neurosci Nurs* 2006, 38:222-226.
8. Turner AP, Williams RM, Sloan AP, Haselkorn JK: Injection anxiety remains a long-term barrier to medication adherence in multiple sclerosis. *Rehabil Psychol* 2009, 54:116-121.
9. Patti F: Optimizing the benefit of multiple sclerosis therapy: the importance of treatment adherence. *Patient Prefer Adherence* 2010, 4:1-9.
10. Cox D, Stone J: Managing self-injection difficulties in patients with relapsing-remitting multiple sclerosis. *J Neurosci Nurs* 2006, 38:167-171.
11. Mohr DC, Boudewyn AC, Likosky W, Levine E, Goodkin DE: Injectable medication for the treatment of multiple sclerosis: the influence of self efficacy expectations and injection anxiety on adherence and ability to self-inject. *Ann Behav Med* 2001, 23:125-132.
12. Lugaresi A: Addressing the need for increased adherence to multiple sclerosis therapy: can delivery technology enhance patient motivation? *Expert Opin Drug Deliv* 2009, 6:995-1002.
13. Rubin RR, Peyrot M: Quality of life, treatment satisfaction, and treatment preference associated with use of a pen device delivering a premixed 70/30 insulin aspart suspension (aspart protamine suspension/soluble aspart) versus alternative treatment strategies. *Diabetes Care* 2004, 27:2495-2497.
14. Summers KH, Szeinbach SL, Lenox SM: Preference for insulin delivery systems among current insulin users and nonusers. *Clin Ther* 2004, 26:1498-1505.
15. Hornquist JO, Wikby A, Andersson PO, Dufva AM: Insulin-pen treatment, quality of life and metabolic control: retrospective intra-group evaluations. *Diabetes Res Clin Pract* 1990, 10:221-230.
16. Mikol D, Lopez-Bresnahan M, Taraskiewicz S, Chang P, Rangnow J: A randomized, multicentre, open-label, parallel-group trial of the tolerability of interferon beta-1a (Rebif) administered by autoinjection or manual injection in relapsing-remitting multiple sclerosis. *Mult Scler* 2005, 11:585-591.
17. Kozubski W: Autoinjector Improves Injection-related Tolerability Issues in Patients with Multiple Sclerosis - Exploring the New Extaviject™ 30G System for the Injection of Interferon Beta-1b. *Eur Neurol Rev* 2010, 5(2):77-81.
18. Lugaresi A, Durastanti V, Gasperini C, Lai M, Pozzilli C, Orefice G, Sotgiu S, Pucci E, Ardito B, Millefiorini E: Safety and tolerability in relapsing-remitting multiple sclerosis patients treated with high-dose subcutaneous interferon-beta by Rebiject autoinjection over a 1-year period: the CoSa study. *Clin Neuropharmacol* 2008, 31:167-172.
19. Brochet B, Lemaire G, Beddiaf A: Reduction of injection site reactions in multiple sclerosis (MS) patients newly started on interferon beta 1b therapy with two different devices. *Rev Neurol (Paris)* 2006, 162:735-740.
20. Freedman SM, Cox D, Rosebrough T: A prospective baseline versus on treatment study assessing patient perceptions of using a smaller needle when injecting intramuscular interferon beta-1 a (Avonex). *J Neurosci Nurs* 2008, 40:350-355.
21. Poland GA, Borrud A, Jacobson RM, McDermott K, Wollan PC, Brakke D, Charboneau JW: Determination of deltoid fat pad thickness. Implications for needle length in adult immunization. *JAMA* 1997, 277:1709-1711.
22. Song TT, Nelson MR, Chang JH, Engler RJ, Chowdhury BA: Adequacy of the epinephrine autoinjector needle length in delivering epinephrine to the intramuscular tissues. *Ann Allergy Asthma Immunol* 2005, 94:539-542.
23. Gibney MA, Arce CH, Byron KJ, Hirsch LJ: Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. *Curr Med Res Opin* 2010, 26:1519-1530.
24. Frid A, Hardebo JE: The thigh may not be suitable as an injection site for patients self-injecting sumatriptan. *Neurology* 1997, 49(2):559-61.

Pre-publication history
The pre-publication history for this paper can be accessed here:
http://www.biomedcentral.com/1471-2377/11/126/prepub

doi:10.1186/1471-2377-11-126
Cite this article as: Phillips *et al.*: An open-label, multicenter study to evaluate the safe and effective use of the single-use autoinjector with an Avonex® prefilled syringe in multiple sclerosis subjects. *BMC Neurology* 2011 11:126.